

Claims

1. A method for attaching a non-corneocyte, nonlabeling, agent to a body tissue comprising:

5 applying to the body tissue a conjugate of the agent and a linking molecule having a carboxamide, the linking molecule being a carboxamide-bearing substrate of transglutaminase,

applying to the body tissue transglutaminase in an amount effective for crosslinking the conjugate to the body tissue via the linking group, and

10 allowing said crosslinking to occur.

2. The method of claim 1, wherein the linking molecule is a molecule selected from the group consisting of:

- (a) at least one glutamine,
- 15 (b) at least two contiguous linked glutamines,
- (c) at least three contiguous linked glutamines,
- (d) at least four contiguous linked glutamines, and
- (e) at least five contiguous linked glutamines.

20 3. The method of claim 1, wherein the linking molecule comprises 5 or more contiguous glutamines attached directly to one another by peptide bonds.

4. The method of claim 1, wherein the linking molecule comprises a polymer of amino acids and wherein at least 20% of the amino acids are glutamines.

25 5. The method of claim 4, wherein at least 30% of the amino acids are glutamines.

6. The method of claim 4, wherein at least 40% of the amino acids are glutamines.

30 7. The method of claim 1, further comprising first attaching to the body tissue a complementary linking molecule bearing multiple reactive aliphatic amines, the complementary linking molecule being an aliphatic amine substrate of transglutaminase,

wherein the conjugate is crosslinked to the body tissue by crosslinking the aliphatic amines of the complementary linking molecule and the carboxamide of linking molecule to one another by said transglutaminase.

5 8. The method of claim 7, wherein the complementary linking molecule is attached to the body tissue by

applying to the body tissue the complementary linking molecule,

applying to the body tissue an amount of transglutaminase effective for crosslinking the complementary linking molecule to the body tissue, and

10 allowing said crosslinking to occur.

9. The method of claim 8, wherein a polymer rich in glutamine is the linking molecule and a polymer rich in lysine is the complementary linking molecule.

15 10. The method of claim 9, wherein the polymer rich in glutamine has 4 or more contiguous glutamines directly attached to one another by peptide bonds.

11. The method of claim 9, wherein the polymer rich in lysine has 4 or more contiguous lysines directly attached to one another by peptide bonds.

20 12. The method of claim 1, wherein the agent is not itself a substrate of transglutaminase.

13. The method of claim 1, wherein the body tissue is selected from the group consisting of the integument, skin, hair and nails, a wound bed, and internal body tissue.

25 14. The method of claim 1, wherein the body tissue is selected from the group consisting of skin, hair and nails, and wherein the agent is selected from the group consisting of a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a sunscreen agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a
30 vitamin, an insect repellent, a coloring agent, a pharmaceutical agent, a ligand-receptor complex and a receptor of a ligand-receptor complex.

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15. The method of claim 1, wherein the nonlabeling active agent is an enzyme.

16. The method of claim 15, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

17. The method of claim 14, wherein the bond between the agent and the linking molecule is hydrolyzable under normal physiological conditions.

18. The method of claim 1, wherein the agent is a nonprotein.

19. The method of claim 18, wherein the agent is not itself a substrate for transglutaminase.

20. A method for attaching an agent to a body tissue comprising
first attaching to the body-tissue a linking molecule that is covalently bondable to the agent in the presence of transglutaminase, then
applying to the body tissue having the linking molecule attached thereto an agent that is a substrate of transglutaminase and that is covalently bondable to the linking molecule in the presence of transglutaminase,
applying to the body tissue transglutaminase in an amount effective in crosslinking the agent to the linking molecule, and
allowing said crosslinking to occur.

21. The method of claim 20, wherein the linking molecule is a substrate of transglutaminase and wherein the linking molecule is attached to the body tissue by
applying to the body tissue the linking molecule,
applying to the body tissue transglutaminase in an amount effective to crosslinking the linking molecule to the body tissue, and
allowing said crosslinking to occur.

22. The method of claim 20, wherein the linking molecule is a polymer having multiple units which carry a carboxamide that is a substrate of transglutaminase.

23. The method of claim 22, wherein a polymer rich in glutamine is the linking molecule.

24. The method of claim 20, wherein the linking molecule is a polymer having multiple units which carry an aliphatic amine that is a substrate of transglutaminase.

25. The method of claim 24, wherein a polymer rich in lysine is the linking molecule.

26. The method of claim 22, wherein the agent comprises a polymer having multiple units which carry an aliphatic amine that is a substrate of transglutaminase.

27. The method of claim 26, wherein the agent comprises a polymer rich in lysine.

28. The method of claim 24, wherein the agent comprises a polymer having multiple units which carry a carboxamide that is a substrate of transglutaminase.

29. The method of claim 28, wherein the agent comprises a polymer rich in glutamine.

30. The method of claim 20, wherein the agent is selected from the group consisting of a visible label of a high affinity noncovalent coupling pair, a pharmaceutical agent, a receptor or a ligand of a receptor/ligand pair, a cosmetic, a sunscreen agent, a coloring agent, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin and an insect repellent.

31. The method of any one of claim 20, wherein the body tissue is selected from the group consisting of the integument, skin, hair, nails, a wound bed, and an internal tissue.

32. A method for attaching an agent to a body tissue comprising
first attaching to the body tissue a linking molecule that is covalently bonded to the agent in the presence of transglutaminase, then
applying to the body tissue having the linking molecule attached thereto an agent that is a substrate of transglutaminase and that is covalently bonded to the linking molecule in the presence of transglutaminase, said applying being carried out in the presence of a sufficient

amount of transglutaminase effective to covalently crosslink the agent to the linking molecule,
and

allowing the crosslinking to occur.

33. The method of claim 32, wherein the linking molecule is a polymer having multiple units which carry a carboxamide that is a substrate of transglutaminase.

34. The method of claim 33, wherein the linking molecule is a polymer rich in glutamine.

35. The method claim 33, wherein the agent comprises a polymer having multiple units which carry an aliphatic amine that is a substrate of transglutaminase.

36. The method of claim 33, wherein the agent comprises a polymer rich in lysine.

37. The method of claim 32, wherein the linking molecule is a polymer having multiple units which carry an aliphatic amine that is a substrate of transglutaminase.

38. The method of claim 32, wherein the linking molecule is a polymer rich in lysine.

39. The method of claim 37, wherein the agent comprises a polymer having multiple units which carry a carboxamide that is a substrate of transglutaminase.

40. The method of claim 37, wherein the agent comprises a polymer rich in glutamine.

41. The method of claim 32, wherein the agent is selected from the group consisting of: a visible label; a component of a high affinity noncovalent coupling pair; a receptor or a ligand of a receptor ligand complex; a pharmaceutical agent, a cosmetic agent, a sunscreen agent, a bulking agent, a hair conditioning agent, a hair fixative, a coloring agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin and an insect repellent

42. The method of claim 32, wherein the body tissue is selected from the group consisting

of: skin; hair; nails; a wound bed; and an internal tissue.

43. A method for sealing tissue comprising applying a force to hold two tissues in contact with each other in the presence of an amount of transglutaminase effective to crosslink the two tissues to one another.

44. The method of claim 43, wherein surfaces of the tissues to be sealed to one another are contacted with a substrate of transglutaminase, which substrate is crosslinked to the surfaces of the tissues to interconnect the surfaces to one another.

45. The method of claim 43, further comprising;

first applying to the surfaces to be linked to one another linking molecules that are a substrate of transglutaminase, in the presence of an amount of transglutaminase effective to crosslink the linking molecules to said surfaces, and

wherein the two tissues are crosslinked to one another by crosslinking the linking molecules to one another by applying to the treated surfaces complementary linking molecules that are a substrate of transglutaminase,

wherein the linking molecules and complementary linking molecules are crosslinked to one another by transglutaminase.

46. A method for attaching a nonextracellular matrix protein, agent to a body tissue comprising:

applying to the body tissue a conjugate of the agent and a linking molecule, the linking molecule being a polymer carrying at least 3 aliphatic amines spaced along the polymer,

applying to the body tissue transglutaminase in an amount effective for crosslinking the linking molecule to the body tissue, and
allowing the crosslinking to occur.

47. The method of claim 46, wherein the linking molecule is selected from the group consisting of at least 3, at least 4 and at least 5 contiguous lysines attached directly to one another by peptide bonds.

48. The method of claim 46, wherein the linking molecule is a polymer of amino acids and wherein the amino acids are selected from the group of: at least 20% of the amino acids are lysines, at least 30% of the amino acids are lysines, and at least 40% of the amino acids are lysines.

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49. The method of claim 46, wherein the agent is selected from the group consisting of: a component of a high affinity noncovalent coupling pair; a receptor or a ligand of a receptor ligand complex; a pharmaceutical agent, a cosmetic agent, a sunscreen agent, a bulking agent, a hair conditioning agent, a hair fixative, a coloring agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin and an insect repellent

50. The method of claim 46, wherein the body tissue is selected from the group consisting of: skin; hair; nails; a wound bed; and an internal tissue.

15 51. The method of claim 46, wherein the agent is not itself a substrate of transglutaminase.

52. The method of claim 46, wherein the agent is a nonprotein.

53. A composition of matter comprising:

20 a conjugate of a nonextracellular matrix, nonlabeling agent and linking molecule having a carboxamide, the linking molecule being a carboxamide-bearing substrate of transglutaminase,

25 wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, a bulking agent, a hair conditioning agent, a hair fixative, a coloring agent, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellent and a component of a high affinity noncovalent coupling pair, and

wherein the linking molecule is not native to the agent.

30 54. The composition of claim 53, wherein the linking molecule comprises at least 5 linked units, each unit being a carboxamide-bearing substrate for transglutaminase.

55. The composition of claim 54, wherein the linking molecule is selected from the group consisting of:

- (a) at least one glutamine,
- (b) at least two linked glutamines,
- (c) at least three linked glutamines,
- (d) at least four linked glutamines, and
- (e) at least five linked glutamines.

56. The composition of claim 53, wherein the linking molecule is 4 or more contiguous glutamines attached directly to one another by peptide bonds.

57. The composition of claim 53, wherein the linking molecule comprises a polymer of amino acids and wherein the amino acids are selected from the group consisting of: at least 20% of the amino acids are glutamines, at least 30% of the amino acids are glutamines, and at least 40% of the amino acids are glutamines.

58. The composition of claim 53, wherein the linking molecule is a polymer rich in glutamine.

59. The composition of claim 53, wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic agent, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, an insect repellent, an enzyme, a coloring agent, a pharmaceutical agent, a ligand of a ligand-receptor complex, a receptor of a ligand-receptor complex, and a component of a high affinity noncovalent binding pair.

60. The composition of claim 59, wherein the agent is selected from the group consisting of a cholinesterase and a phosphodiesterase.

61. The composition of claim 53, wherein the bond between the agent and the linking molecule is hydrolyzable under physiological conditions.

62. The composition of claim 59, wherein the agent is a pharmaceutical agent and the bond between the agent and the linking molecule is hydrolyzable under physiological conditions.

5 63. The composition of claim 53, wherein the agent is a nonprotein.

64. The composition of claim 53, wherein the agent in its native form free of conjugation to the linking molecule is not itself a substrate of transglutaminase.

10 65. A composition of matter comprising:
a conjugate of a nonextracellular matrix, nonlabeling agent and a polymer having multiple units carrying a polyaliphatic amine that is a substrate of transglutaminase,
wherein the agent is selected from the group consisting of a sunscreen agent, a cosmetic, an enzyme, a bulking agent, a hair conditioning agent, a hair fixative, a moisturizing
15 agent, a depilatory agent, an anti-nerve gas agent, a film forming agent, a vitamin, a coloring agent, a pharmaceutical agent, a member of a ligand/receptor pair, a tissue sealant, an insect repellant and a component of a high affinity noncovalent coupling pair, and
wherein the polymer carries at least 3 aliphatic amines spaced at discrete intervals along the polymer.

20 66. The composition of matter of claim 65, wherein the polymer comprises at least 3, at least 4 or at least 5 contiguous lysines attached to one another by peptide bonds.

25 67. The composition of matter of claim 65, wherein the polymer comprises amino acids, and wherein at least 20%, at least 30% or at least 40% of the amino acids are lysines.

68. The compositions of matter of claim 65, wherein the bond between the agent and the linking molecule is hydrolyzable under physiological conditions.

30 69. The composition of matter of claim 65, wherein the agent is a nonprotein.

70. The composition of matter of claim 65, wherein the agent in its native form, free of

conjugation to the linking molecule, is not itself a substrate of transglutaminase.

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71. A kit comprising
a package housing:

5 a first container containing the composition of any one of claims 53, 54, 55, 56, 57, 58,
59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69 and 70, and
a second container containing transglutaminase.

72. The kit of claim 71, further comprising

10 a third container housed by said package, the third container containing a linking
molecule that is a substrate of transglutaminase and that is covalently attached to the
composition contained in the first container, if in the presence of transglutaminase.

73. The kit of claim 71, further comprising calcium housed by said package, except that
15 said calcium is not in said second container.

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